CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-274

CORRESPONDENCE

BIOAVAILABILITY

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

FEB 27 1998

GRG AMENDMENT
AB

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCE AMENDMENT

RE: HYDROXYCHLOROQUINE SULFATE TABLETS, USP
200 MG
ANDA 40-274
RESPONSE TO AGENCY CORRESPONDENCE DATED JANUARY 16, 1998

Dear Mr. Sporn:

Reference is made to the ANDA identified above, which is currently under review, and to the January 16, 1998 letter pertaining to this application which was forwarded to Mylan from the Office of Generic Drugs' Division of Bioequivalence. In response to the January 16 correspondence, Mylan wishes to amend the application as follows:

A. REGARDING BIOEQUIVALENCE ISSUES:

FDA COMMENT 1. The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in U.S.P. 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

RECEIVED
MAR 2 1998
GENERIC DRUGS

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 599-7284
Human Resources (304) 598-5406
Information Systems (304) 285-6404
Label Control (800) 848-0463
Legal Services (304) 598-5408
Maintenance & Engineering (304) 598-5411
Medical Unit (304) 598-5445
Quality Control (304) 598-5401
Research & Development (304) 598-5407
Sales & Marketing (304) 285-6409
(304) 598-3232

MYLAN RESPONSE: The dissolution testing requested by the Division of Bioequivalence will be incorporated into Mylan's stability and quality control programs as of the date of this amendment. This testing is identical to that which was previously proposed in the original ANDA for the above referenced product which was submitted on August 28, 1997.

It is also acknowledged and understood that the bioequivalency comments expressed in the letter dated January 16, 1998 are preliminary and may be revised after review of the entire application.

For your reference, a copy of the Agency correspondence dated January 16, 1998 is enclosed.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

FOR

Frank R. Sisto
Executive Director
Regulatory Affairs

FRS/tlm

enclosures

ANDA 40-274

Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
Morgantown, WV 26504-4310

SEP 30 1997

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to your correspondence dated September 19, 1997.

NAME OF DRUG: Hydroxychloroqine Sulfate Tablets USP, 200 mg

DATE OF APPLICATION: August 28, 1997

DATE OF RECEIPT: August 29, 1997

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Joseph Buccine
Project Manager
(301) 827-5848

Sincerely yours,

/s/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

SEP 19 1997

Office of Generic Drugs, CDER, FDA
Doglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT
RE: HYDROXYCHLOROQUINE SULFATE TABLETS, USP 200MG
ANDA 40-274

Dear Mr. Sporn:

Reference is made to the pending Abbreviated New Drug Application identified above and to a September 19, 1997 phone call form the Agency regarding this application.

As pointed out by the Agency reviewer the heading at the top of page 23, located in Volume 1, Section IV, incorrectly referenced the wrong drug product. As this page is duplicated in Section V, the heading on page 156 is also incorrect. This amendment provides for replacement pages 23A and 156A, which have been revised to correct the drug product name in the heading. No other changes have been made.

As required by 21 CFR 314.96(b) we certify that a true copy of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to FDA's Baltimore District Office.

Should you have any questions regarding this amendment or require additional information please contact the undersigned by phone at (304) 599-2595, ext. 6600 or by facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Executive Director,
Regulatory Affairs

FRS/bad

enclosures

RECEIVED
SEP 22 1997
GENERIC DRUGS

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
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Information Systems (304) 285-6404
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Maintenance & Engineering (304) 598-5411
Medical Unit (304) 598-5445
Purchasing (304) 598-5401
Quality Control (304) 598-5407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

AUG 28 1997

ELECTRONIC DATA ENCLOSED
BIOEQUIVALENCE DATA ENCLOSED

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: HYDROXYCHLOROQUINE SULFATE TABLETS, USP 200 MG

Dear Mr. Sporn:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR § 314.92 and 314.94, we submit the enclosed abbreviated new drug application for:

Proprietary Name: None
Established Name: Hydroxychloroquine Sulfate Tablets, USP
This application consists of a total of 19 volumes.
- Archival Copy - 8 volumes.
- Review Copy - 9 volumes.
  - Technical Section For Chemistry - 2 volumes.
  - Technical Section For Pharmacokinetics - 7 volumes.
- Analytical Methods - 2 extra copies; 1 volume each.

NOTE: The Technical Section for Pharmacokinetics of the review copy and the archival copy each contain a data diskette for the bioequivalence study.

This application provides for the manufacture of Hydroxychloroquine Sulfate Tablets, USP 200 mg. All operations in the manufacture, packaging, and labeling of the drug product are performed by Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road, Morgantown, WV 26505-2730.

As required by 21 CFR 314.94(d)(5) we certify that a true copy of the technical sections of this application as submitted to the Office of Generic Drugs has been forwarded to the FDA's Baltimore District Office. The following Reader's Guide and Table of Contents detail the documentation submitted in support of this application.

All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310.

Sincerely,

Frank R. Sisto
Executive Director
Regulatory Affairs

FRS/tlm

RECEIVED
AUG 29 1997
GENERIC DRUGS

Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Business Development	(304) 599-7284	Legal Services	(304) 598-5408	Research & Development	(304) 285-6409
Human Resources	(304) 598-5406	Maintenance & Engineering	(304) 598-5411	Sales & Marketing	(304) 598-3232
		Medical Unit	(304) 598-5445		

ORIG AMENDMENT
N/AM

MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

APR - 1 1998

TELEPHONE AMENDMENT

RE: HYDROXYCHLOROQUINE SULFATE TABLETS, USP 200 MG
ANDA #40-274
MINOR AMENDMENT DATED FEBRUARY 27, 1998

Dear Mr. Sporn:

Reference is made to the pending application and minor amendment identified above and to the Agency call dated March 09, 1998. In the call dated March 09, 1998, Mylan was requested to provide notification to the Agency of the date of reply from the drug substance DMF holder in which the deficiencies for DMF 8619 were to be addressed with the Agency. Mylan has been notified by the DMF holder for Hydroxychloroquine Sulfate that the deficiencies for DMF vere addressed in a submission to the Agency dated March 31, 1998 (see attached correspondence). This letter serves as notification to the Agency that the DMF deficiencies have been addressed by the holder as of March 31, 1998, and in conjunction with the previously submitted correspondence identified above (Minor Amendment dated February 27, 1998), provide for a complete response to the Agency's letter of January 16, 1998.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is being submitted in duplicate. An additional copy is being provided by facsimile to Mr. Joe Buccine of the Office of Generic Drugs. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Laura Weirigg/for

Frank R. Sisto
Executive Director
Regulatory Affairs

FRS/tlm

enclosures

cc: Joe Buccine, Project Manager (via facsimile)
Office of Generic Drugs
Division of Labeling and Program Support
Chemistry - Branch 1

APR 0 2 1998

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Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
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Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445		

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

FEB 27 1998

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

RE: HYDROXYCHLOROQUINE SULFATE TABLETS, USP
200 MG
ANDA #40-274
RESPONSE TO AGENCY CORRESPONDENCE DATED JANUARY 16, 1998

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above which is currently under review, and to the comments from the Agency regarding this application which were forwarded to Mylan by facsimile on January 16, 1998. With regard to the January 16 comments, Mylan wishes to amend this application with the following:

A. REGARDING CHEMISTRY ISSUES:

B. REGARDING MISCELLANEOUS ISSUES:

FDA COMMENT 1. The firms referenced in your application must be in compliance with CGMPs at the time of approval.

MYLAN RESPONSE: Mylan acknowledges that the firms referenced in the application must be in compliance with CGMPs at the time of approval.

C. REGARDING LABELING ISSUES:

MYLAN RESPONSE: Attachment L contains twelve (12) copies of the following final printed bottle labels and package outserts for Hydroxychloroquine Sulfate Tablets, USP, 200 mg.

BOTTLE LABELS

200 mg 100 tablets Code - RM0373A

PACKAGE OUTSERT

Code - **HXCQ:R1**; revised JANUARY 1998

The enclosed labeling incorporates the revisions requested in the Agency's letter dated January 16, 1998. Copies of this letter is provided in Attachment J for the convenience of the reviewer.

In order to facilitate the review of this labeling and in accordance with 21 CFR 314.94(a)(8)(iv), Attachment K contains a side-by-side comparison of the final printed labeling to the labeling that was previously submitted. It is noted that prior to approval of this application the agency reserves the right to request further changes in the Mylan labeling based upon the changes in the approved labeling of the listed drug or upon further review of the application.

Prior to the printing of production quantities of the labeling, Mylan commits to revise the labeling pursuant to the FDA Modernization Act of 1997, Section 126 and FDA Guidance for Industry entitled "Implementation of Section 126, Elimination of Certain Labeling Requirements, of the Food and Drug Administration Modernization Act of 1997" (February 1998). The Federal Caution will be replaced by the phrase "**℞ only**". On the bottle labels "**℞ only**" will appear on the bottom right corner of the center panel. "**℞ only**" will appear at the end of the package outsert directly above the Mylan logo.

D. REGARDING BIOEQUIVALENCE ISSUES:

FDA COMMENT 1. The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in U.S.P. 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

MYLAN RESPONSE: The above comment from the Division of Bioequivalence dated January 16, 1998 has been addressed in a separate amendment to the application and was forwarded to the Office of Generic Drugs on February 27, 1998.

In response, Mylan submits that the dissolution testing requested by the Division of Bioequivalence will be incorporated into Mylan's stability and quality control programs as of the date of this amendment. The dissolution testing is identical to that which was previously proposed in the original ANDA for the above referenced product which was submitted on August 28, 1997.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic drugs, has been forwarded to the FDA's Baltimore District Office.

For your reference, a copy of the Agency correspondence dated January 16, 1998, is enclosed as Attachment J.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

FOR

Frank R. Sisto
Executive Director
Regulatory Affairs

FRS/tlm

enclosures

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-274 APPLICANT: Mylan

DRUG PRODUCT: Hydroxychloroquine Sulfate U.S.P. 200 mg tablets

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in U.S.P. 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUE

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-274 APPLICANT: Mylan

DRUG PRODUCT: Hydroxychloroquine Sulfate U.S.P. 200 mg tablets

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in U.S.P. 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

[S]

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-274 APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Hydroxychloroquine Sulfate Tablets USP, 200 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. DMF for hydroxychloroquine sulfate drug substance was found inadequate. The DMF holder has been notified of the deficiencies. Please provide notification in your response that the DMF holder has responded to these deficiencies.

2. Please identify the known impurities/degradants and report the individual values for the related substances in the finished product and stability. Also, identify the known impurities/degradants and include in the finished product and stability specification.

3. Please set a specification and perform tapped density on the drug substance.

4. Please indicate if the product will be packaged in any other size container/closure systems since your stability protocol indicates testing in the largest and smallest container system.

5. Please tighten the hardness specification or justify the wide range.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The firms referenced in your application must be in compliance with CGMPs at the time of approval.

Sincerely yours,

/S/ 1/4/4

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research